## REMARKS

Claims 24-33 and 41-52 are pending. Claim 50 has been allowed. New claims 51-52 has support in original claims 25 and 42, and in the specification at p. 7, lines 14-16; and p. 8, lines 6-13. Amendments to the claims are shown in the attached Appendix, "MARKED UP VERSION TO SHOW CHANGES MADE." A list of the pending claims is attached as Appendix II for the Examiner's convenience.

**Rejection under 35 U.S.C. § 112, first paragraph (Written Description)**

The Examiner has rejected claims 24-33 and 41-49 under 35 U.S.C. 112, first paragraph, as containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention at the time of filing the application.

The Examiner argues that the term "homolog" includes mammalian ATPases. Applicants have amended Claim 24 to clarify that the homologs are Mycobacterial homologs. Applicants respectfully request that the rejection be withdrawn.

**Rejection under 35 U.S.C. § 112, first paragraph (Enablement)**

The Examiner has also rejected claims 24-33 and 41-49 under 35 U.S.C. 112, first paragraph, stating that the specification does not reasonably provide enablement for a method of detecting the presence of antibodies to all Mycobacteria. Applicants respectfully traverse.

The claims recite a method using SEQ ID NO:2, a homolog thereof, or an antigenic determinant thereof to detect a Mycobacterium in a sample. Applicants have shown that the antigen encoded by SEQ ID NO:2 is absent from avirulent forms of mycobacteria (*see* page 28, lines 24-27; page 30, lines 9-13), while it is present in virulent forms. Thus, it is reasonable to expect that a homolog of SEQ ID NO: 2 will be recognized by antibodies directed against a homolog of SEQ ID NO:2 from a virulent form of mycobacteria.

Applicants again point out that homologs of SEQ ID NO:2 are absent from avirulent forms of Mycobacterium (*M. vaccae* and *M. smegmatis*), supporting a reasonable conclusion that the protein (or its homolog) is found in pathogenic forms of Mycobacterium, but not in non-pathogenic forms. Based on this, one of skill in the art would reasonably conclude that the virulent mycobacteria *M. leprae, M. africanum, M. microti, M. avium, M. intracellulare* and *M. scrofulaceum* each encode a homolog of SEQ ID NO:2, and that the homolog can react with Mycobacterial antibodies against the homolog to detect an immune response to infection by any of these species of mycobacteria.

Applicants wish to clarify that the statement in the prior response that the protein encoded by SEQ ID NO:2 does not react with "other" antibodies (see page 6, end of first paragraph, response dated July 2, 2001) refers to the non-reactivity with previously known antigens (p.20, lines 8-19), not to reactivity to homologs of SEQ ID NO:2. The statement was provided to explain that the antibody is highly specific, in support of enablement.

Applicants submit that one of ordinary skill in the art, upon reading the specification, would have a reasonable expectation of practicing all of the claimed subject matter.

Applicants maintain that an immune response of a TB-infected patient can be detected by combining a biological sample, such as patients' sera, with SEQ ID NO:2, a homolog of SEQ ID NO:2, or an antigenic determinant of SEQ ID NO:2. (See page 11, lines 7-20).

Applicants submit that the claims are in proper form for allowance and request that the rejection be withdrawn.

## CONCLUSION

Applicants submit that the claims are in form for allowance. If the Examiner believes there are any remaining issues that may be addressed by telephone, she is requested to contact the undersigned attorney at (415) 781-1989.

Respectfully submitted,

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## APPENDIX I: MARKED UP VERSION TO SHOW CHANGES MADE

24. (Amended) A method of detecting the presence of antibodies to virulent Mycobacterium in a biological sample, said method comprising:

combining said sample with a protein having the amino acid sequence of SEQ ID NO:2, a Mycobacterial homolog thereof or an antigenic determinant thereof; and

detecting antibodies bound to said protein;

wherein said Mycobacterium is *M. bovis, M. tuberculosis, M. leprae, M. africanum, M. microti, M. avium, M. intracellulare* or *M. scrofulaceum*.

25. (Amended) The method of Claim 24, wherein said [virulent] Mycobacterium is [selected the group consisting of] *M. bovis[, M. tuberculosis, M. leprae, M. africanum, M. microti, M. avium, M. intracellulare* and *M. scrofulaceum].*

41. (Amended) A method of detecting the presence of Mycobacterium in a biological sample, said method comprising;

lysing the cells in said sample;

combining said lysate with antibodies to a protein having the amino acid sequence of SEQ ID NO:2 or an antigenic determinant thereof; and

detecting said antibodies bound to protein in said lysate;

wherein said Mycobacterium is *M. bovis, M. tuberculosis, M. leprae, M. africanum, M. microti, M. avium, M. intracellulare* or *M. scrofulaceum.*

42. (Amended) The method of Claim 41, wherein said Mycobacterium is [selected from the group consisting of] *M. bovis[, M. tuberculosis, M. leprae, M. africanum, M. microti, M. avium, M. intracellulare* and *M. scrofulaceum].*

## APPENDIX II: PENDING CLAIMS

24. (Amended) A method of detecting the presence of antibodies to virulent Mycobacterium in a biological sample, said method comprising:
combining said sample with a protein having the amino acid sequence of SEQ ID NO:2, a Mycobacterial homolog thereof or an antigenic determinant thereof; and
detecting antibodies bound to said protein;
wherein said Mycobacterium is *M. bovis, M. tuberculosis, M. leprae, M. africanum, M. microti, M. avium, M. intracellulare* or *M. scrofulaceum.*

25. (Amended) The method of Claim 24, wherein said Mycobacterium is *M. bovis.*

26. The method of Claim 24, wherein said protein is immobilized on a solid support.

27. The method of Claim 26, wherein said solid support is nitrocellulose.

28. The method of Claim 24, wherein said sample comprises one or more of sputum, blood, and serum.

29. The method of Claim 24, wherein said detecting is by a qualitative detection system.

30. The method of Claim 29, wherein said qualitative detection system is a horseradish peroxidase-protein A detection system.

31. The method of Claim 24, wherein said detecting is by a quantitative detection system.

32. The method of Claim 31, wherein said quantitative detection system is a radioimmunoassay.

33. The method of Claim 24, further comprising:
combining a control biological sample with said protein; and
comparing the detection of said binding to the binding of antibodies in the control sample with said protein.

41. (Amended) A method of detecting the presence of Mycobacterium in a biological sample, said method comprising;
lysing the cells in said sample;
combining said lysate with antibodies to a protein having the amino acid sequence of SEQ ID NO:2 or an antigenic determinant thereof; and
detecting said antibodies bound to protein in said lysate;
wherein said Mycobacterium is *M. bovis, M. tuberculosis, M. leprae, M. africanum, M. microti, M. avium, M. intracellulare* or *M. scrofulaceum.*

42. (Amended) The method of Claim 41, wherein said Mycobacterium is *M. bovis*.

43. The method of Claim 41, wherein said lysate is immobilized on a solid support.

44. The method of Claim 43, wherein said solid support is nitrocellulose.

45. The method of Claim 41, wherein said detecting is by a qualitative detection system.

46. The method of Claim 45, wherein said qualitative detection system is a horseradish peroxidase-protein A detection system.

47. The method of Claim 41, wherein said detecting is by a quantitative detection system.

48. The method of Claim 47, wherein said quantitative detection system is a radioimmunoassay.

49. The method of Claim 41, further comprising:
culturing a diagnostic sample to produce colonies of bacteria present therein, whereby said culture represents said biological sample.

50. A method of detecting the presence of antibodies to a virulent Mycobacteriam in a biological sample, said method comprising:
combining said sample with a purified protein of a mycobacterium other than *M. bovis* BCG, wherein said protein is a homolog of the protein of SEQ ID NO:2; is an immunogenic membrane-associated protein of said mycobacterium; and is encoded by DNA which is capable of hybridizing with a DNA probe having the complete sequence represented in SEQ ID NO: 1 under conditions where, on a Southern blot, said probe will identify single 3.25 kb BamHI fragments from *M. bovis* BCG and *M. tuberculosis* H37Rv DNA, but will not hybridize with BamHI-digested DNA from either *M. smegmatis* or *M. vaccae*.

51. (New) The method of Claim 24, wherein said Mycobacterium is *M. tuberculosis*.

52. (New) The method of Claim 41, wherein said Mycobacterium is *M. tuberculosis*.